```
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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  DEC 23   New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                   USPAT2
 NEWS  4  JAN 13   IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS  5  JAN 13   New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                   INPADOC
 NEWS  6  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS  7  JAN 17   IPC 8 in the WPI family of databases including WPIFV
 NEWS  8  JAN 30   Saved answer limit increased
 NEWS  9  FEB 21   STN AnaVist, Version 1.1, lets you share your STN AnaVist
                   visualization results
 NEWS 10  FEB 22   The IPC thesaurus added to additional patent databases on STN
 NEWS 11  FEB 22   Updates in EPFULL; IPC 8 enhancements added
 NEWS 12  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS 13  FEB 28   MEDLINE/LMEDLINE reload improves functionality
 NEWS 14  FEB 28   TOXCENTER reloaded with enhancements
 NEWS 15  FEB 28   REGISTRY/ZREGISTRY enhanced with more experimental spectral
                   property data
 NEWS 16  MAR 01   INSPEC reloaded and enhanced
 NEWS 17  MAR 03   Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS 18  MAR 08   X.25 communication option no longer available after June 2006
 NEWS 19  MAR 22   EMBASE is now updated on a daily basis
 NEWS 20  APR 03   New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 21  APR 03   Bibliographic data updates resume; new IPC 8 fields and IPC
                   thesaurus added in PCTFULL
 NEWS 22  APR 04   STN AnaVist $500 visualization usage credit offered
 NEWS 23  APR 12   LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 24  APR 12   Improved structure highlighting in FQHIT and QHIT display
                   in MARPAT
 NEWS 25  APR 12   Derwent World Patents Index to be reloaded and enhanced during
                   second quarter; strategies may be affected

 NEWS EXPRESS  FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8

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* * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *
```

```
FILE 'HOME' ENTERED AT 15:04:48 ON 26 APR 2006

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 15:04:57 ON 26 APR 2006
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DICTIONARY FILE UPDATES:  25 APR 2006  HIGHEST RN 881879-55-6

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\09786998.str

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l1 sss sam
SAMPLE SEARCH INITIATED 15:05:42 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        2 TO ITERATE

100.0% PROCESSED        2 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            2 TO      124
```

```
PROJECTED ANSWERS:                0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 exact
SAMPLE SEARCH INITIATED 15:05:55 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED        0 ITERATIONS                                 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L3             0 SEA EXA SAM L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 3.96       4.17

FILE 'CAPLUS' ENTERED AT 15:10:16 ON 26 APR 2006
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FILE COVERS 1907 - 26 Apr 2006  VOL 144 ISS 18
FILE LAST UPDATED: 25 Apr 2006  (20060425/ED)

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They are available for your review at:

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=> s l1 and doxorubicin
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




SAMPLE SEARCH INITIATED 15:10:34 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        2 TO ITERATE

100.0% PROCESSED        2 ITERATIONS                                 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            2 TO      124
PROJECTED ANSWERS:               0 TO        0

L4             0 SEA SSS SAM L1
```

```
L5            0 L4


          14715 DOXORUBICIN
             28 DOXORUBICINS
          14717 DOXORUBICIN
                  (DOXORUBICIN OR DOXORUBICINS)
L6            0 L5 AND DOXORUBICIN

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     7.47      12.54

FILE 'REGISTRY' ENTERED AT 15:17:32 ON 26 APR 2006
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STRUCTURE FILE UPDATES:   25 APR 2006  HIGHEST RN 881879-55-6
DICTIONARY FILE UPDATES:  25 APR 2006  HIGHEST RN 881879-55-6

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\09786998-1.str

L7      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l7 sss sam
SAMPLE SEARCH INITIATED 15:18:09 FILE 'REGISTRY'
```

SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED 2 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 2 TO 124
PROJECTED ANSWERS: 0 TO 0

L8 0 SEA SSS SAM L7

=> s l7 sss full
FULL SEARCH INITIATED 15:18:35 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 94 TO ITERATE

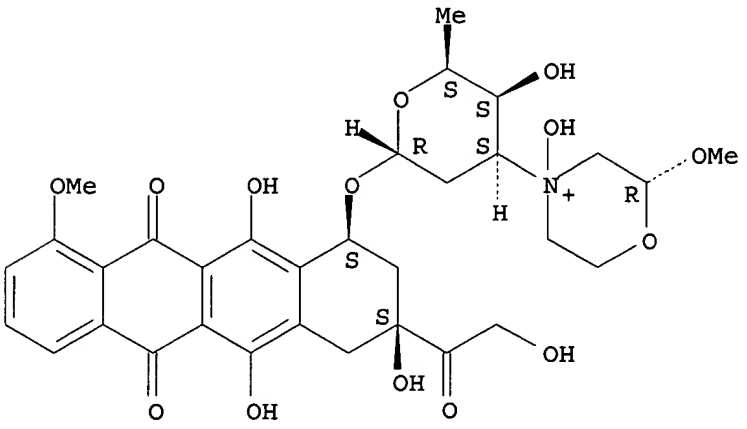
100.0% PROCESSED 94 ITERATIONS 32 ANSWERS
SEARCH TIME: 00.00.01

L9 32 SEA SSS FUL L7

=> d scan

L9 32 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2R)-4-hydroxy-2-methoxymorpholinium-4-yl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-(9CI)
MF C32 H38 N O14
CI COM

Absolute stereochemistry.



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> s l1 sss full
FULL SEARCH INITIATED 15:19:30 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 91 TO ITERATE

100.0% PROCESSED 91 ITERATIONS 21 ANSWERS
SEARCH TIME: 00.00.01

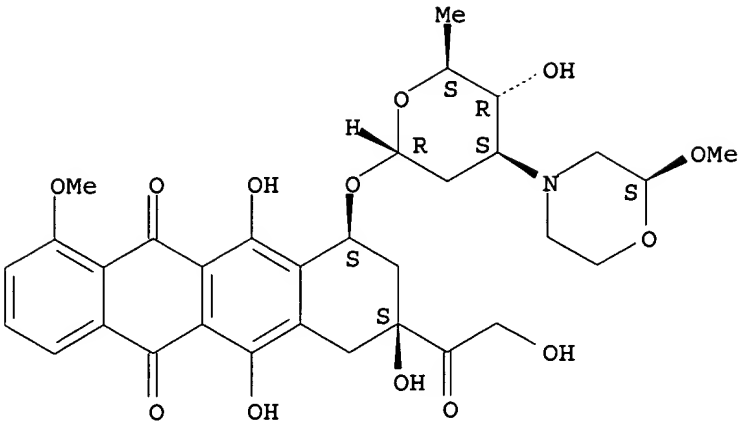
L10 21 SEA SSS FUL L1

=> d scan

L10 21 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-(2-methoxy-4-morpholinyl)-α-L-arabino-hexopyranosyl]oxy]-, [8S-[8α,10α(R*)]]-(9CI)

MF C32 H37 N O13

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	334.76	347.30

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FILE LAST UPDATED: 25 Apr 2006 (20060425/ED)

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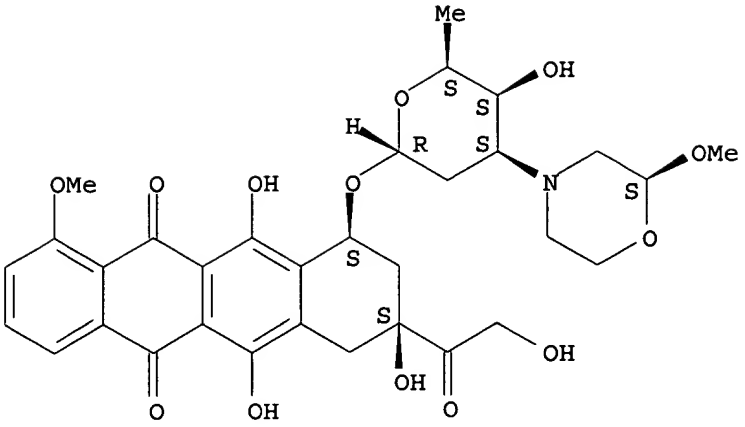
They are available for your review at:

http://www.cas.org/infopolicy.html

```
=> s l10 and doxorubicin
            92 L10
         14715 DOXORUBICIN
            28 DOXORUBICINS
         14717 DOXORUBICIN
                  (DOXORUBICIN OR DOXORUBICINS)
L11         72 L10 AND DOXORUBICIN

=> s l10 and MMDX
            92 L10
            16 MMDX
L12         14 L10 AND MMDX
```

```
=> s l12 and tumor
        368685 TUMOR
        145721 TUMORS
        415113 TUMOR
                  (TUMOR OR TUMORS)
L13           9 L12 AND TUMOR

=> dis l13 1-9 bib abs hitstr

L13  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2005:180849  CAPLUS
DN   143:482
TI   Formation and antitumor activity of PNU-159682, a major metabolite of
     nemorubicin in human liver microsomes
AU   Quintieri, Luigi; Geroni, Cristina; Fantin, Marianna; Battaglia,
     Rosangela; Rosato, Antonio; Speed, William; Zanovello, Paola; Floreani,
     Maura
CS   Department of Pharmacology and Anesthesiology, Pharmacology Section,
     University of Padua, Padua, Italy
SO   Clinical Cancer Research (2005), 11(4), 1608-1617
     CODEN: CCREF4; ISSN: 1078-0432
PB   American Association for Cancer Research
DT   Journal
LA   English
AB   Nemorubicin (3'-deamino-3'-[2''(S)-methoxy-4''-morpholinyl]doxorubicin;
     MMDX) is an investigational drug currently in phase II/III clin.
     testing in hepatocellular carcinoma.  A bioactivation product of
     MMDX, 3'-deamino-3'',4'-anhydro-[2''(S)-methoxy-3''(R)-oxy-4''-
     morpholinyl]doxorubicin (PNU-159682), has been recently identified in an
     incubate of the drug with NADPH-supplemented rat liver microsomes.  The
     aims of this study were to obtain information about MMDX
     biotransformation to PNU-159682 in humans, and to explore the antitumor
     activity of PNU-159682.  Human liver microsomes (HLM) and microsomes from
     genetically engineered cell lines expressing individual human cytochrome
     P450s (CYP) were used to study MMDX biotransformation.  We also
     examined the cytotoxicity and antitumor activity of PNU-159682 using a panel
     of in vitro-cultured human tumor cell lines and tumor
     -bearing mice, resp.  HLMs converted MMDX to a major metabolite,
     whose retention time in liquid chromatog. and ion fragmentation in tandem
     mass spectrometry were identical to those of synthetic PNU-159682.  In a
     bank of HLMs from 10 donors, rates of PNU-159682 formation correlated
     significantly with three distinct CYP3A-mediated activities.
     Troleandomycin and ketoconazole, both inhibitors of CYP3A, markedly
     reduced PNU-159682 formation by HLMs; the reaction was also
     concentration-dependently inhibited by a monoclonal antibody to CYP3A4/5.  Of the
     10 cDNA-expressed CYPs examined, only CYP3A4 formed PNU-159682.  In addition,
     PNU-159682 was remarkably more cytotoxic than MMDX and
     doxorubicin in vitro, and was effective in the two in vivo tumor
     models tested, i.e., disseminated murine L1210 leukemia and MX-1 human
     mammary carcinoma xenografts.  CYP3A4, the major CYP in human liver,
     converts MMDX to a more cytotoxic metabolite, PNU-159682, which
     retains antitumor activity in vivo.
IT   108852-90-0, Nemorubicin
     RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
     activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (CYP3A4, major cytochrome P 450 in human liver microsome converted
        MMDX to metabolite PNU-159682 which retained cytotoxic,
        antitumor activity in human tumor cell line and tumor
        -bearing mouse)
RN   108852-90-0  CAPLUS
CN   5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-
     (hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-
     morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI)  (CA
     INDEX NAME)

Absolute stereochemistry.
```

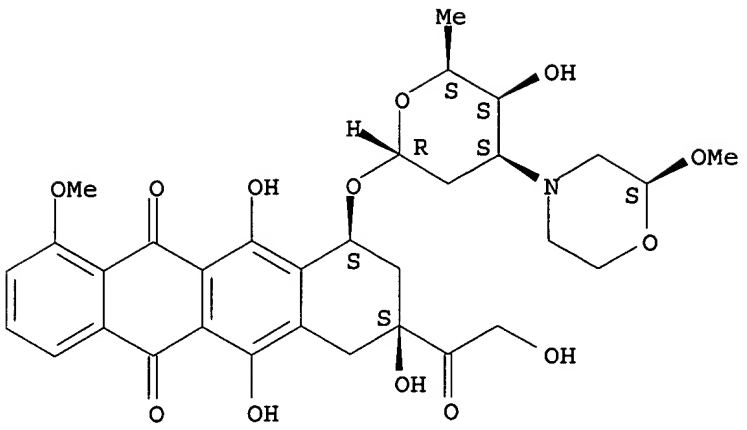


RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:52993 CAPLUS
DN 142:190557
TI Antitumor activity of methoxymorpholinyl doxorubicin: Potentiation by cytochrome P450 3A metabolism
AU Lu, Hong; Waxman, David J.
CS Division of Cell and Molecular Biology, Department of Biology, Boston University, Boston, MA, USA
SO Molecular Pharmacology (2005), 67(1), 212-219
CODEN: MOPMA3; ISSN: 0026-895X
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Methoxymorpholinyl doxorubicin (**MMDX**) is a novel liver cytochrome P 450 (P 450)-activated anticancer prodrug whose toxicity toward cultured **tumor** cells can be potentiated up to 100-fold by incubation with liver microsomes and NADPH. In the present study, a panel of human liver microsomes activated **MMDX** with potentiation ratios directly correlated to the CYP3A-dependent testosterone 6β-hydroxylase activity of each liver sample. Microsome-activated **MMDX** exhibited nanomolar IC50 values in growth-inhibition assays of human **tumor** cell lines representing multiple tissues of origin: lung (A549 cells), brain (U251 cells), colon (LS180 cells), and breast (MCF-7 cells). Anal. of individual cDNA-expressed CYP3A enzymes revealed that rat CYP3A1 and human CYP3A4 activated **MMDX** more efficiently than rat CYP3A2 and that human P450s 3A5 and 3A7 displayed little or no activity. **MMDX** cytotoxicity was substantially increased in Chinese hamster ovary cells after stable expression of CYO3A4 in combination with P 450 reductase. CYP3A activation of **MMDX** abolished the parent drug's residual cross-resistance in a doxorubicin-resistant MCF-7 cell line that overexpresses P-glycoprotein. CYP3A-activated **MMDX** displayed a comparatively high intrinsic stability, with a t1/2 of .apprx.5.5 h at 37°. **MMDX** was rapidly activated by CYP3A at low (.apprx.1-5 nM) prodrug concns., with 100% **tumor** cell kill obtained after as short as a 2-h exposure to the activated metabolite. These findings demonstrate that **MMDX** can be activated by CYP3A metabolism to a potent, long-lived, and cell-permeable cytotoxic metabolite and suggest that this anthracycline prodrug may be used in combination with CYP3A4 in a P 450 prodrug activation-based gene therapy for cancer treatment.
IT **108852-90-0**, Methoxymorpholinyldoxorubicin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of methoxymorpholinyl doxorubicin and potentiation by cytochrome P 450 3A metabolism)
RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA

INDEX NAME)

Absolute stereochemistry.

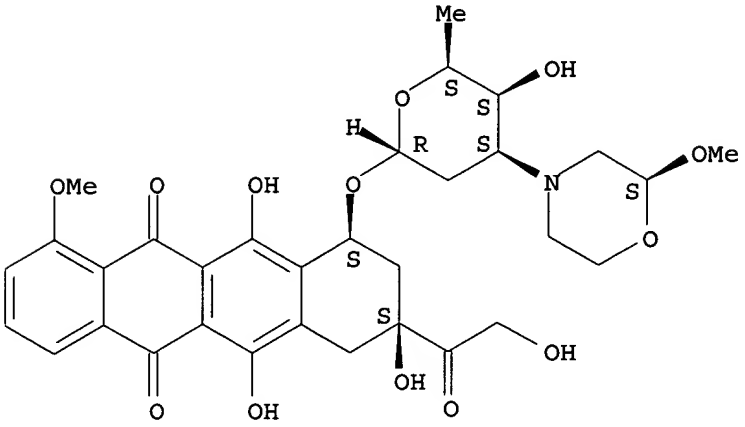


RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:961148 CAPLUS
DN 138:378512
TI Identification of novel enzyme-prodrug combinations for use in cytochrome P450-based gene therapy for cancer
AU Baldwin, Alex; Huang, Zeqi; Jounaidi, Youssef; Waxman, David J.
CS Department of Biology, Division of Cell and Molecular Biology, Boston University, Boston, MA, 02215, USA
SO Archives of Biochemistry and Biophysics (2002), Volume Date 2003, 409(1), 197-206
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier Science
DT Journal
LA English
AB Gene-directed enzyme prodrug therapy can be used to increase the therapeutic activity of anti-cancer prodrugs that undergo liver cytochrome P 450 (CYP)-catalyzed prodrug to active drug conversion. The present report describes a cell-culture-based assay to identify CYP gene-CYP prodrug combinations that generate bystander cytotoxic metabolites and that may potentially be useful for CYP-based gene therapy for cancer. A panel of rat liver microsomes, comprising distinct subsets of drug-inducible hepatic CYPs, was evaluated for prodrug activation in a four-day 9L gliosarcoma cell growth inhibition assay. A strong NADPH- and liver microsome-dependent increase in 9L cytotoxicity was observed for the CYP prodrugs cyclophosphamide, ifosfamide, and methoxymorpholinyl doxorubicin (**MMDX**) but not with three other CYP prodrugs, procarbazine, dacarbazine, and tamoxifen. **MMDX** activation was potentiated .apprx.250-fold by liver microsomes from dexamethasone-induced rats (IC50 (**MMDX**) .apprx.0.1 nM), suggesting that dexamethasone-inducible CYP3A enzymes contribute to activation of this novel anthracycline anti-**tumor** agent. This CYP3A dependence was verified in studies using liver microsomes from uninduced male and female rats and by using the CYP3A-selective inhibitors troleandomycin and ketoconazole. These findings highlight the advantages of using cell culture assays to identify novel CYP prodrug-CYP gene combinations that are characterized by production of cell-permeable, cytotoxic metabolites and that may potentially be incorporated into CYP-based gene therapies for cancer treatment.
IT **108852-90-0**, PNU-152243
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of novel enzyme-prodrug combinations for use in cytochrome P 450-based gene therapy for cancer)
RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-

(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:438786 CAPLUS
DN 133:144561
TI In vivo antitumor activity and host toxicity of methoxymorpholinyl doxorubicin: role of cytochrome P450 3A
AU Quintieri, Luigi; Rosato, Antonio; Napoli, Eleonora; Sola, Francesco; Geroni, Cristina; Floreani, Maura; Zanovello, Paola
CS Oncology Section, Department of Oncology and Surgical Sciences, University of Padova, Padua, 35128, Italy
SO Cancer Research (2000), 60(12), 3232-3238
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Methoxymorpholinyl doxorubicin (**MMDX**; PNU 152243) is a promising doxorubicin derivative currently undergoing clin. evaluation. Previous in vitro studies suggested that the compound undergoes hepatic biotransformation by cytochrome P 450 (CYP) 3A into a more cytotoxic metabolite(s). The present study examined the role of CYP3A-mediated metabolism in the in vivo antitumor activity and host toxicity of **MMDX** in the mouse model and investigated the potential for increasing the therapeutic effectiveness of the drug by inducing its hepatic CYP-catalyzed activation. We found that **MMDX** cytotoxicity for cultured M5076 **tumor** cells was potentiated 22-fold by preincubating the drug with NADPH-supplemented liver microsomes from untreated C57BL/6 female mice. A greater (50-fold) potentiation of **MMDX** cytotoxicity was observed after its preincubation with liver microsomes isolated from animals pretreated with the prototypical CYP3A inducer pregnenolone-16α-carbonitrile. In contrast, in vivo administration of the selective CYP3A inhibitor troleandomycin (TAO) reduced both potentiation of **MMDX** cytotoxicity and the rate of CYP3A-catalyzed N-demethylation of erythromycin by isolated liver microsomes (55.5 and 49% reduction, resp.). In vivo antitumor activity expts. revealed that TAO completely suppressed the ability of 90 μg/kg **MMDX** i.v., a dose close to the LD10, to delay growth of s.c. M5076 **tumors** in C57BL/6 mice and to prolong survival of DBA/2 mice with disseminated L1210 leukemia. Moreover, TAO administration markedly inhibited the therapeutic efficacy of 90 μg/kg **MMDX** i.v. in mice bearing exptl. M5076 liver metastases; a complete loss of **MMDX** activity was observed in liver metastases-bearing animals receiving 40 μg/kg **MMDX** i.v. plus TAO. However, pregnenolone-16α-carbonitrile pretreatment failed to enhance **MMDX** activity in mice bearing either s.c. M5076 **tumors**

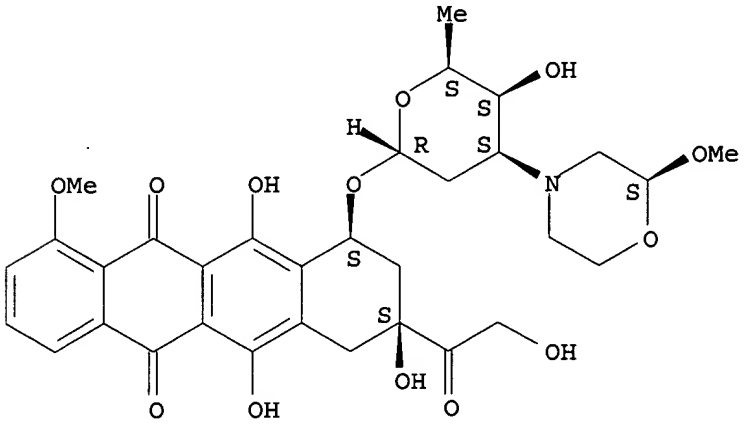
or exptl. M5076 liver metastases. Addnl. expts. carried out in healthy C57BL/6 mice showed that TAO markedly inhibited **MMDX**-induced myelosuppression and protected the animals against LDs of **MMDX**. Taken together, these findings demonstrate that an active metabolite(s) of **MMDX** synthesized via CYP3A contributes significantly to its in vivo antitumor activity and host toxicity.

IT **108852-90-0**, PNU 152243
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antitumor activity and host toxicity of methoxymorpholinyl doxorubicin: role of cytochrome P 450 3A)

RN 108852-90-0 CAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:191827 CAPLUS
DN 130:320537
TI The antitumor efficacy of cytotoxic drugs is potentiated by treatment with PNU 145156E, a growth-factor-complexing molecule
AU Sola, Francesco; Capolongo, L.; Moneta, Donatella; Ubezio, Paolo; Grandi, Maria
CS Pharmacia Upjohn, Milan, I-20014, Italy
SO Cancer Chemotherapy and Pharmacology (1999), 43(3), 241-246
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer-Verlag
DT Journal
LA English
AB PNU 145156E (formerly FCE 26644) is a non-cytotoxic mol. whose antitumor activity is exerted through the formation of a reversible complex with growth/angiogenic factors, thus inhibiting their induction of angiogenesis. The in vitro and in vivo the activity of PNU 145156E was studied in combination with the 4 cytotoxic drugs doxorubicin, cyclophosphamide, methoxy-morpholinyl-doxorubicin (**MMDX**, FCE 23762, PNU 152243), and 9-aminocamptothecin against M5076 murine reticulosarcoma. In vitro, PNU 145156E did not modify the cytotoxicity of the 4 drugs or the cell-cycle block induced by doxorubicin. In vivo, at the optimal dose of each compound, the antitumor activity was increased in all combinations, with no associated increase in general toxicity being observed In healthy mice treated with cyclophosphamide or doxorubicin the association with PNU 145156E did not enhance the myelotoxic effect induced by the 2 cytotoxics. These results indicate that 2 drugs affecting solid **tumor** growth through 2 different mechanisms - growth factor

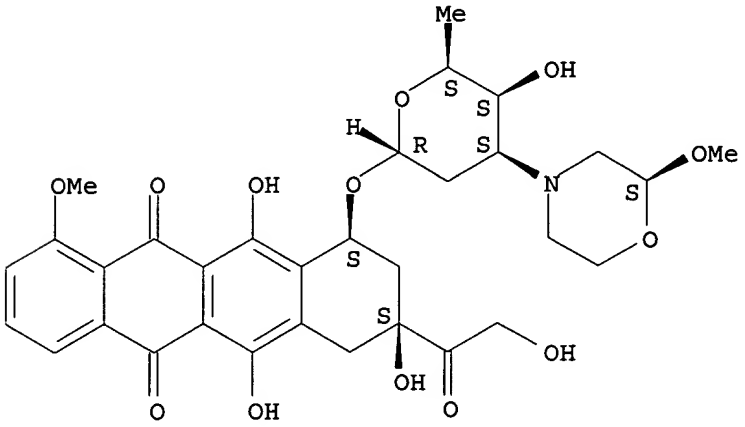
blockage and cell proliferation - can be combined, resulting in increased antitumor efficacy with no additive toxicity.

IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor efficacy of cytotoxic drugs is potentiated by treatment with PNU 145156E)

RN 108852-90-0 CAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1999:186967 CAPLUS

DN 131:39313

TI Delivery of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells: effect in mice bearing hepatic metastases

AU Quintieri, L.; Rosato, A.; Amboldi, N.; Vizler, C.; Ballinari, D.; Zanovello, P.; Collavo, D.

CS Department of Oncology and Surgical Sciences, University of Padova, Padua, 35128, Italy

SO British Journal of Cancer (1999), 79(7/8), 1067-1073
CODEN: BJCAAI; ISSN: 0007-0920

PB Churchill Livingstone

DT Journal

LA English

AB The possibility of using interleukin 2 (IL-2)-activated natural killer cells (A-NK) to carry methoxymorpholinyl doxorubicin (**MMDX**; PNU 152243) to liver-infiltrating **tumors** was explored in mice bearing 2-day established M5076 reticulum cell sarcoma hepatic metastases. In vitro, **MMDX** was 5.5-fold more potent than doxorubicin against M5076 **tumor** cells. **MMDX** uptake by A-NK cells correlated linearly with drug concentration in the incubation medium [correlation coefficient (r) = 0.999]; furthermore, as **MMDX** incorporation was readily reproducible in different expts., the amount of drug delivered by A-NK cells could be modulated. In vivo expts. showed that i.v. injection of **MMDX**-loaded A-NK cells exerted a greater therapeutic effect than equivalent or even higher doses of free drug. The increase in lifespan (ILS) following A-NK cell delivery of 53 μg kg-1 **MMDX**, a dosage that is ineffective when administered in free form, was similar to that observed in response to 92 μg kg-1 free drug, a dosage close to the 10% LD (ILS 42% vs. 38%, resp.). These results correlated with pharmacokinetic studies showing that **MMDX** encapsulation in A-NK cells strongly modifies its organ distribution and targets it to tissues in which IL-2-activated lymphocytes are preferentially entrapped after

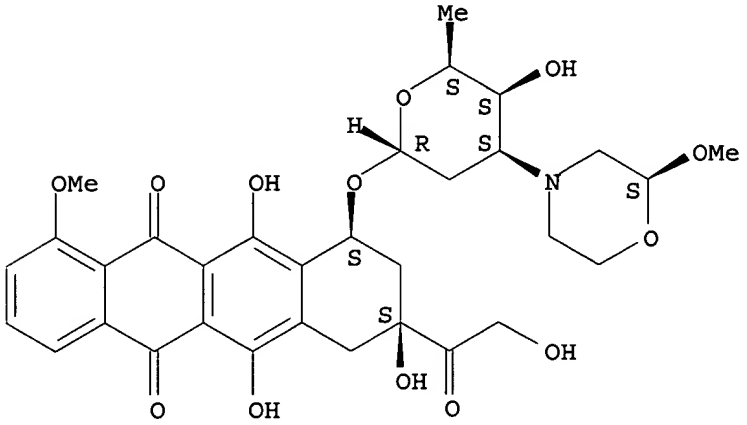
i.v. injection.

IT **108852-90-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(delivery of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells and its effect in mice bearing hepatic metastases)

RN 108852-90-0 CAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1998:468189 CAPLUS

DN 129:211400

TI Hematotoxicity on human bone marrow- and umbilical cord blood-derived progenitor cells and in vitro therapeutic index of methoxymorpholinyldoxorubicin and its metabolites

AU Ghielmini, Michele; Colli, Emilia; Bosshard, Giovanna; Pennella, Giulia; Geroni, Cristina; Torri, Valter; D'Incalci, Maurizio; Cavalli, Franco; Sessa, Cristiana

CS Servizio Oncologico Cantonale, Ospedale S. Giovanni, Bellinzona, CH-6500, Switz.

SO Cancer Chemotherapy and Pharmacology (1998), 42(3), 235-240
CODEN: CCPHDZ; ISSN: 0344-5704

PB Springer-Verlag

DT Journal

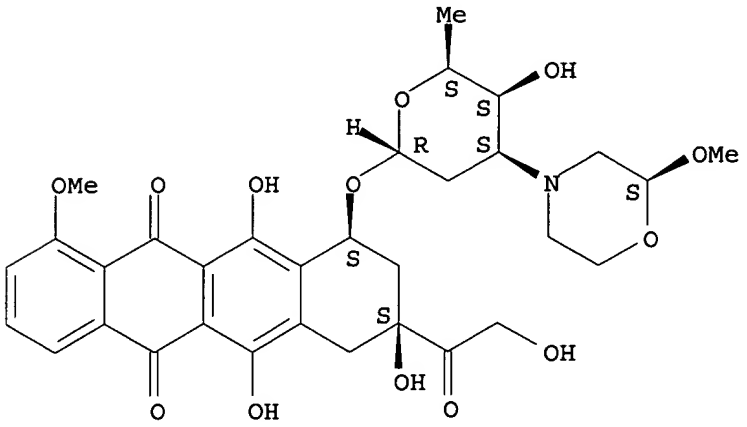
LA English

AB The toxic concentration of a 1-h period of exposure to doxorubicin (DX), {3'-deamino-3'-[2(S)-methoxy-4-morpholinyl]doxorubicin} (**MMDX**), and bioactivated **MMDX** on hematopoietic progenitors and **tumor** cell lines was determined in vitro. Human bone marrow (BM) cells were twice as sensitive as human cord blood-derived (hCB) clonogenic cells to cytotoxics, and **MMDX** was twice as toxic as DX against hCB cells. **MMDX** activated with normal rat liver microsomes and with dexamethasone-induced rat microsomes, resp. were 70 and 230 times more toxic than **MMDX**. DX and **MMDX** had 5-fold stronger activities on **tumor** cell lines than on granulocyte/macrophage colony-forming cells, whereas bioactivated **MMDX** showed comparable cytotoxicity against **tumor** cells and hematopoietic progenitors. **MMDX** metabolites were very potent but displayed a lower degree of **tumor** selectivity than **MMDX**.

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(methoxymorpholinyldoxorubicin and its metabolites hemotoxicity on

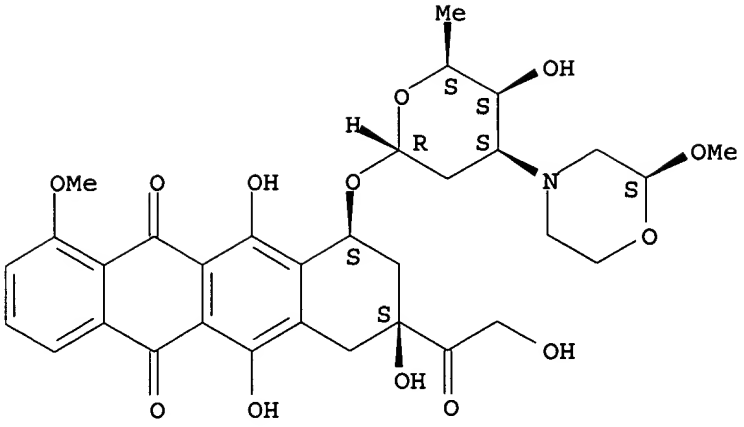
human bone marrow- and umbilical cord blood-derived progenitor cells)
RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



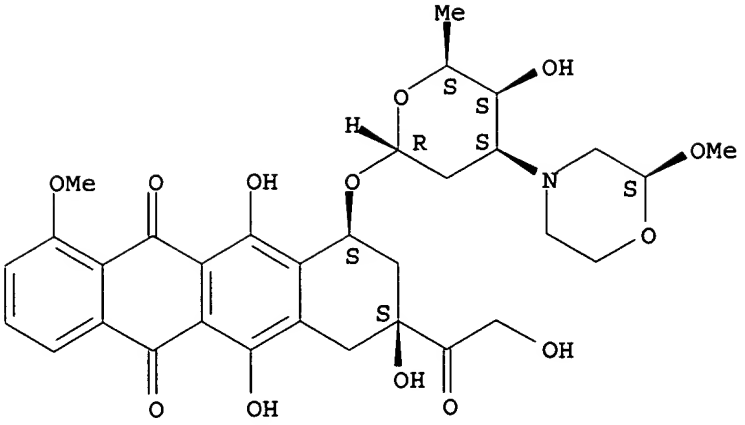
L13 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1995:291513 CAPLUS
DN 122:95727
TI Analysis of intracellular retention of morpholinyl anthracyclines in multidrug resistant cancer cells by interactive laser cytometry
AU Lau, Derick H. M.; Duran, George E.; Sikic, Branimir I.
CS Davis Cancer Center, University California, Sacramento, CA, 95817, USA
SO International Journal of Oncology (1994), 5(6), 1273-7
CODEN: IJONES; ISSN: 1019-6439
DT Journal
LA English
AB Interactive laser cytometry was applied to measure intracellular fluorescence of doxorubicin (DOX) accumulation in a uterine sarcoma cell line, MES-SA and a series of multidrug resistant sublines, Dx0.3, Dx1 and Dx5. Exposure of each cell line to 10 μM DOX for 2 h resulted in an intracellular fluorescent level directly correlated to its sensitivity to the drug but inversely related to its cellular P-glycoprotein (P-gp) level. The morpholinyl anthracyclines, methoxymorpholinyl DOX (**MMDX**) and morpholinyl DOX (MRA), were equally highly cytotoxic against the multidrug sensitive and resistant cancer cells. After exposure to 10 μM of **MMDX** or MRA for 2 h, the multidrug resistant cells, Dx5, retained as much intracellular fluorescence as the multidrug sensitive cells, MES-SA. In the resistant cells, the intracellular fluorescence of **MMDX** or MRA was 8 fold higher than that of DOX. Interactive laser- cytometer is a useful tool for screening cancer cells with the MDR phenotype and for identifying new anthracyclines effective against drug resistant malignancies.
IT **108852-90-0**
RL: ANT (Analyte); ANST (Analytical study)
(anal. of intracellular retention of morpholinylanthracyclines in multidrug resistant cancer cells by interactive laser cytometry)
RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



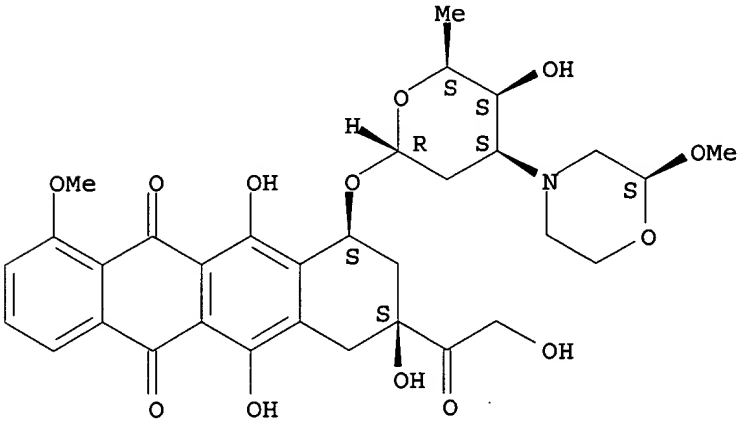
L13 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1994:621172 CAPLUS
DN 121:221172
TI Effects of the methoxymorpholino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow
AU Kuhl, Jorn-Sven; Duran, George E.; Chao, Nelson J.; Sikic, Branimir I.
CS Oncol. Div., Stanford Univ. Sch. Med., Stanford, CA, 94305, USA
SO Cancer Chemotherapy and Pharmacology (1993), 33(1), 10-16
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
AB The methoxymorpholino derivative of doxorubicin (**MMDX**; FCE 23762) has recently entered clin. trials because of its broad spectrum of preclin. antitumor activity and non-cross-resistance in multidrug-resistant (MDR) **tumor** models. **MMDX** is activated in the liver to a >10 times more potent metabolite that cross-links DNA. To assess the potential of this drug in hematol. malignancies, we studied the myelotoxicity in vitro and antitumor effect of **MMDX** as well as its bioactivated form (**MMDX**+) in a panel of 14 different human leukemia and lymphoma cell lines. The **tumor** specificity of **MMDX** in CEM and K562 cells was similar to that of doxorubicin (DOX), and that of **MMDX**+ was slightly superior. All of the 14 cell lines were found to be more sensitive to **MMDX** and **MMDX**+ than were granulocyte-macrophage progenitors. On a molar basis, **MMDX** was approx. 3-100 times more active than DOX, and **MMDX**+ was 10-1,000 times more potent than DOX. The cytotoxic effect of **MMDX** and **MMDX**+ in two P-glycoprotein-pos. MDR sublines was greatly improved in comparison with that of DOX. Whereas the response to DOX in the different leukemia and lymphoma cell lines was highly heterogeneous, the response to **MMDX** and **MMDX**+ was rather homogeneous. The novel anthracycline **MMDX** and its bioactivated from **MMDX**+ are highly active against this panel of human leukemia and lymphoma cell lines and demonstrate potentially greater selectivity for **tumor** cells in vitro as compared with normal bone marrow precursors.
IT **108852-90-0**, FCE 23762 **108852-90-0D**, FCE 23762, active metabolite
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(leukemia and lymphoma inhibition by and myelotoxicity of doxorubicin and its methoxymorpholino derivative in human cell lines)
RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 108852-90-0 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L1 STRUCTURE UPLOADED
L2 0 S L1 SSS SAM
L3 0 S L1 EXACT

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S L1 AND DOXORUBICIN

FILE 'REGISTRY' ENTERED AT 15:10:33 ON 26 APR 2006
L4 0 S L1

FILE 'CAPLUS' ENTERED AT 15:10:34 ON 26 APR 2006
L5 0 S L4
L6 0 S L5 AND DOXORUBICIN

FILE 'REGISTRY' ENTERED AT 15:17:32 ON 26 APR 2006
L7 STRUCTURE UPLOADED
L8 0 S L7 SSS SAM
L9 32 S L7 SSS FULL
L10 21 S L1 SSS FULL

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L11 72 S L10 AND DOXORUBICIN

L12 14 S L10 AND MMDX

L13 9 S L12 AND TUMOR